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Letter to the Editor: "Secondary Cancers After Ewing Sarcoma and Ewing Sarcoma as Second Malignant Neoplasm"

The development of a second malignant neoplasm (SMN) is the most devastating event after the successful treatment of childhood cancer. Several studies have estimated an increased (22–35%) cumulative risk of secondary cancers following Ewing sarcoma [1,2]. Radiation-induced osteosarcoma and therapy-related acute myeloid leukemia (AML) are the most frequent SMNs, although malignant fibrous histiocytoma, breast carcinoma, and other common tumours in adults have been described [1–7]. In a recent review from three institutions, 16 cases of SMN were reported among 266 survivors of Ewing sarcoma [3]. Most of these tumours developed within previously irradiated fields, and a radiation dose-dependency was found to be evident for secondary sarcomas. In contrast, Ewing sarcoma has rarely been observed as a SMN, with only about 15 such cases reported [8]. While most of these occurrences were associated with retinoblastoma [9], isolated cases have been reported following treatment of other tumours like large cell lymphoma or Wilms tumour [8,10]. No cases of Ewing sarcoma were found among 91 secondary bone sarcomas from the Late Effects Study Group [11].

A retrospective review was undertaken of 121 patients with Ewing sarcoma of bone or soft tissue and primitive neuroectodermal tumours seen in our single centre from 1970 through 1995. The purpose was to ascertain the incidence of second cancers. Primary treatment consisted of systemic multiagent chemotherapy plus local irradiation, wide surgery, or both. Forty-two (35%) patients were alive and disease-free more than 3 years after diagnosis. Table I summarizes the characteristics of 4 patients found to have a SMN after the treatment of Ewing sarcoma. Case 3 has been previously reported [12]. One breast carcinoma could be related to local irradiation (whole lung radiation therapy for metastatic disease), whereas both acute leukemias were probably chemotherapy-related. Interestingly, only one case of osteosarcoma was seen occurring in a patient surgically treated for Ewing sarcoma. Moreover, in three other patients Ewing sarcoma developed as a second cancer (Table II). None of them could be related to radiation therapy of the primary tumour. Aside from case 2, who received symptomatic measures, patients were treated with standard protocols and four of them are now alive and disease-free.

Data from the literature indicate that patients with Ewing sarcoma are at a significantly increased risk of SMNs [1,4]. Therapy-related factors (radiotherapy, alkylating agents, and epipodophyllotoxins) have been most often advocated. However, some observations also suggest a genetic tumour predisposition in this population: (1) There is an excess risk of SMNs following Ewing sarcoma in comparison with other childhood cancers [4]; (2) The incidence of Ewing sarcoma as a SMN could be higher than suspected, since such cases are usually excluded from clinical trials; (3) SMNs, including osteosarcoma, have been described in survivors of Ewing sarcoma, which developed outside the irradiation fields of the primary tumour; (4) An inherent relationship between Ewing sarcoma and AML has been suggested, possibly in terms of a common histogenesis [5,13]. Although numbers are small and unrelated coincidence can not be excluded, our experience suggests that there is an intrinsic predisposition to SMNs in patients with Ewing sarcoma and that it is not only a therapy-related matter.

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TABLE I. Second Malignant Neoplasms Among 121 Patients With Ewing Sarcoma*

	Ewing sarcoma				Second cancer	
Patient no.	Age/sex	Site Stage	Treatment	Interval (years)[a]	Histology Site	Current status (months after SMN)
1	11/F	Radius Metastatic	VCR-ADR RT 50 Gy, lung 20 Gy	15	Ductal Ca. Breast	Died of SMN 52
2	6/M	Ribs Metastatic	SUR + RT 30 Gy VCR, ADR, CPA, DACT, CDDP, IFO, DTIC, VP-16, VM-26	9	AML (M2)	Died of SMN 3
3	8/M	Pelvis Localized	SUR CPA, ADR, IFO, VP-16, VCR, DACT, CDDP, VM-26	2.6	AML (M3)	Alive, disease-free 48+
4	10/M	Pelvis Localized	SUR CPA, ADR, VCR, DACT, BCNU	10	Osteosarcoma Femur	Alive, disease-free 9+

*F: female; M: male; RT: radiation therapy; SUR: surgery; Ca: carcinoma; SMN: second malignant neoplasm; AML: acute myeloid leukemia; VCR: vincristine; ADR: doxorubicin; CPA: cyclophosphamide; DACT: dactinomycin; CDDP: cisplatin; IFO: ifosfamide; DTIC: dacarbazine; VP-16: etopside; VM-26: teniposide; BCNU: carmustine.
[a]Interval from diagnosis of primary tumor to diagnosis of second malignancy.

TABLE II. Ewing Sarcoma as Second Malignant Neoplasm*

	Primary tumor				Ewing sarcoma	
Patient no.	Age/sex	Histology Site	Treatment	Interval (years)[a]	Site Stage	Current status (months after SMN)
5	25/M	MFH Scapula	SUR + RT 60 Gy CYVADIC	5.5	Pelvis Localized	Died of SMN 30
6	3/M	ALL	VCR, LAG, ADR, 6-MP, MTX, AraC, Cranial RT	12	Ulna Metastatic	Alive, disease-free 15+
7	11/M	AML (M4)	ADR, DNR, MTZ, AraC, 6-TG, 6-MP, VP-16	7	Fibula Localized	Alive, disease-free 20+

*M: male; MFH: malignant fibrous histiocytoma; RT: radiation therapy; SUR: surgery; SMN: second malignant neoplasm; CYVADIC: cyclophosphamide, vincristine, doxorubicin, and dacarbazine; AML: acute myeloid leukemia; ALL: acute lymphoblastic leukemia; VCR: vincristine; LAG: L-asparaginase; ADR: doxorubicin; AraC: cytarabine; 6-MP: 6-mercaptopurine; MTX: methotrexate; DNR: daunorubicin; MTZ: mitoxantrone; 6-TG: thioguanine; VP-16: etopside.
[a]Interval from diagnosis of primary tumor to diagnosis of second malignancy.

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